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Conference on Comparative Metabolism and Toxicity of Vinyl Chloride-Related Compounds: Overview and Summary

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I suspect that there is little more that can be said about the metabolism and toxicity of halogenated olefins that has not been said at this meeting. Although I have faithfully attended and taken notes on all papers presented here, it would be foolhardy for me to attempt to make either complimentary or critical comments about each and every paper.

In the first session of this conference we learned of factors that influence the tumorogenicity, demonstrated experimentally, not only with the now-infamous vinyl chloride, but also with vinylidene chloride, hexachlorocyclobutadiene, trichloroethylene, and several other related compounds tested in the National Cancer Institute's carcinogen screening program. Clearly, it would seem, the halogenated olefin class of compounds will be considered presumptive carcinogens. Are there ways to predict, short of long-term animal testing, whether or not a particular halogenated olefin represents a carcinogenic hazard? Papers by Drs. Henschler, Hathaway, Van Duuren, Leibman, and Van Dyke dealt with biological activity as a function of chemical and physical-chemical characteristics of compounds. Consideration of these relationships coupled with metabolic considerations may provide testable theoretical proposals for predicting the mutagenic and carcinogenic potential of halogenated aliphatic and olefinic compounds. Papers by Dr. Rosenkrantz and others suggest the usefulness of certain *in vitro* test systems for further evaluating mutagenic and carcinogenic potential.

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Exciting as these possibilities are, several reports at this conference have raised the question as to whether some of the conventional indices of hepato- and nephrotoxicity produced by the halogenated olefins do not also have predictive value. That is, would detection of injury by these indices suffice to indicate the need to prevent exposures which might, at higher doses or longer times, be carcinogenic? Of course, this possibility is only practical if there is assurance that the surveillance of the health of workers or others who might be exposed to these compounds is adequate to detect the early and reversible indices of injury and that such detection leads to correction of the exposure conditions that resulted in early injury. I seriously doubt whether we have a sufficient data base on dose-response and time-response relationships for reversible chemical injury and irreversible events (as carcinogenesis) to adopt such an approach. However, the acquisition of data that may permit evaluation of such possibilities is an obvious area for research and should guide hypothesis formulations and experimental design.

We heard frequent mention of pharmacokinetic considerations as determinants of the toxic responses to halogenated olefins. Are the concepts of saturable metabolic pathways and rate-limiting activation and detoxication reactions sufficiently developed to allow us to decide whether or not effects seen in high-dose acute studies have implications for chronic low-dose exposures? Certainly there seems to be hope in this approach, an approach which may even allow monitoring of urinary excretion of metabolites in exposed workers as a means of determining their susceptibility to injury. However, the practical realization of such potential de-

mands that we know what metabolic pathways are important in producing either more or less toxic or carcinogenic metabolites. Indeed, we may be able to account for as much as 95% of a compound's metabolism, but, if an unidentified metabolite which represents only 1% of the total is the active compound, it will be difficult to convincingly argue that we can evaluate hazard by pharmacokinetic considerations. Nevertheless, the coupling of distribution pharmacokinetics with enzymatic biotransformation kinetics, or with specific target-molecule reaction kinetics, is the only logical means of attempting to move from empirical considerations in safety evaluation to scientific predictive models.

On the topic of multiple pathways of metabolism, the demonstration that the hepatotoxic action of halothane is enhanced under hypoxic conditions adds a new aspect to our considerations of the metabolism-toxicity relationship for this compound. The report and suggestion that a reductive pathway of metabolism may ultimately provide the toxic, reactive metabolite of halothane illustrates that we must not fall into the trap of thinking that microsomal oxidases are the only critical pathways for activation of these compounds. Indeed, four decades ago, it was the enzymatic reduction of prontosil that was one of the first demonstrations of metabolic formation of a more biologically active derivative of an otherwise inactive drug.

Some evidence was presented at this conference that indicates that the low-frequency occurrence of acute hepatotoxicity in humans exposed to halothane and related anesthetics is not, as once thought, a case of allergic response, but may instead be metabolically based. A logical question might be: What genetic or environmental factors contribute to this metabolic uniqueness?

The demonstration, by Dr. Rosenkrantz, of *in vitro* mutagenicity of urine samples from anesthesiology staff is, of course, a provocative observation in view of the apparent association of excess incidence of cancer in these hospital personnel. The possible application of *in vitro* screening methods to detection of presumptive carcinogens in human body fluids will most certainly force the issue of research to corroborate or refute the validity of these tests in the total hazard evaluation process. Perhaps the cytogenetic studies of the type described for vinyl chloride workers by Dr. Purchase will be a part of this evaluation.

We have heard much about covalent binding of halo-olefins and their metabolites. Indeed, nonspecific covalent binding to proteins has served well as a means of detecting the formation of more reactive metabolites. However, we have really little information regarding what percentage of this binding, if any, is to critical biological macromolecules. Several papers pointed out the need to separate nonspecific and noncritical binding from critical target site binding, e.g., to nucleic acids or phospholipids. Similarly, it is obvious that glutathione is an important endogenous modulator of halo-olefin toxicity, at least in part because it provides a conjugating molecule for detoxification. It has been suggested that glutathione may act in other ways to protect reactive SH sites in membranes which may be critical target sites.

In short, we seem to have some ideas, but relatively little convincing demonstration of specific target sites, to explain the acute or chronic, nontumorigenic, toxicity of the halo-olefins. Or does it have to be halo-olefins? Witness Rory Conolly's observation of hepatotoxicity of ethylene in PCB-induced rats.

And what of interactions? Both the tumorigenicity and other cytotoxic or organ toxicity of halo-olefins have been reported at this conference to be modified by numerous factors: both endogenous, e.g. species, age, sex; and exogenous, e.g. diet, other chemicals, ethanol ingestion. How can these influences be predicted or how should they be taken into account in hazard evaluations? I suspect that the answer to that question will come only when we have a more thorough understanding of the mechanisms by which these interactions occur. Attempts to explain interactions have dealt previously with attempting to manipulate the epoxide hydrase metabolism system and the glutathione transferase system. Certainly epoxide formation seems to be a central and critical intermediate in the biological activation of most (if not all) of the halo-olefins. Whether or not the use of inducers or inhibitors of epoxidation and of epoxide hydration will provide insight into mechanisms of toxic interactions of halo-olefins will likely be a subject of continuing investigation in a number of laboratories.

Finally, I think this conference demonstrates that in the last five years—since Dr. Viola's and Dr. Maltoni's first reports of tumorigenic action of vinyl chloride—we have come quite a distance in understanding the comparative toxicity and metabolism of halo-olefins. I think the conference also has illustrated that we have a lot yet to learn.

I want to thank Dr. Falk and the National Institute of Environmental Health Sciences for giving me, all of us, the opportunity to participate in this very comprehensive updating of the toxicology of this important class of chemical compounds. I think Dr. Falk deserves our highest praise and gratitude for identifying and bringing together all those who gave such excellent papers here.

Letter to the Editor

Dear Sir:

Recently I submitted a paper to EHP proposing a guideline for action to protect the public against environmental hazards arising from technological products and processes. I called it the "Primacy Principle." To implement this guideline, I suggested a special format and review procedure for papers presenting new data on technological hazards. The EHP reviewers didn't care for my proposals and unanimously rejected my paper. As one reviewer remarked, "I doubt if EHP, as a purely scientific journal, should go into this administrative and political field."

There was some suggestion that the paper might be more appropriate if it were recast as a "Letter to the Editor" or presented at an APHA conference where a "more immediate consensus" on the proposals would be possible. In what follows, I have tried to follow both suggestions by rewriting the material as a letter and incorporating some of the editorial reactions. Therefore let me start with the original statement of the "Primacy Principle:"

With potential technological hazards to the public health, the "benefit of the doubt" must go to the public and not to the technology.

There seems to be two main objections to the Primacy Principle. One criticism is that it is not "scientific," that is "political" or "subjective." I agree. When (as here) we are dealing with the setting of priorities, we are necessarily outside of the boundaries of "pure science." We are dealing with the value systems of human beings. However I would argue that environmental health is not "pure science." There is no good reason for the public to support such research unless the findings are translated into action programs to protect the public from environmental hazards. Effective action involves setting of priorities. Therefore, the topic, "scientific" or not, seems to me appropriate for a journal called *Environmental Health Perspectives*.

Another objection involves the concept that science is "neutral," that it is neither on the side of the proponents of a potentially hazardous technology nor the side of the public. Insofar as the estimates of hazard are based on sound statistical methods applied to reliable factual evidence—insofar as the estimation is scientific—then the estimates can be objective, unbiased, and neutral. However, it is a fact of life that in any complex actual health issue will not have scientifically valid estimates of all of the relevant benefits and costs. To take action, we eventually must do some guessing. When we talk about the benefit of the doubt we are talking about guesswork, not science.

Guesswork is inherently subjective and this is true even when it is called expert opinion or linear extrapolation or risk-benefit analysis. This is where the benefit of the doubt comes in. When we guess, we can make mistakes in either direction. The Primacy Principle says we should prefer to fail in a direction which will be fail-safe for the public. When we have to guess, we explicitly give the public priority over technology.

A different kind of objection to the Primacy Principle is that it is too vague. This vagueness is inherent in general guidelines and can be reduced by exploring the implications of a general principle. By applying the principle to the troublesome questions about the "burden of proof" in publications on potentially hazardous uses of technology, for example, I suggested the following amplification: Under this principle, the burden of proof is on the health scientist to produce prima facie evidence of hazard. Once this is done the burden of proof shifts to the proponents of a technology to show it is safe.

The evidence needed for a prima facie case is analogous to that required for a grand jury indictment (as opposed to conviction at an actual trial). Thus it is sufficient to present an outline of the data, the methodology, and the conclusions to show that there is a case for the existence of the hazard. The case itself (with full details and discussion) would presumably require a hearing and could not be presented in a single paper. Where possible, references to evidence should be cited rather than reproducing all the material in detail. The argument or rationale should be in plain English rather than in a technical or scientific jargon.

To implement this working rule for determining the burden of proof, some expeditious way of communicating the early warning report (and the prima facie case) to the health scientists and to the public is needed. What I suggested was that some journal (not necessarily EHP) regularly print such early warning reports. This does not mean that any and every warning would be printed. There would have to be new data (or new analyses of previous data) presented that might be considered a prima facie case for environmental hazard. Neither the journal nor the referees would have to accept or endorse the findings. These points could be made very clear in explanatory text introducing the Early Warning Report. It would be up to the readership, and ultimately the public, to judge whether or not a prima facie case had indeed been made.

Since the suggested format for an early warning paper is somewhat different from the traditional formats (for instance, it would not include any extensive literature review), there would have to be

some special editorial processing. Rejection should be based on something specifically wrong with the data or the methodology (and not on general objections or doubts). Precautions would have to be taken against having proponents of the potentially hazardous technology (or their scientific allies) block the publication of early warning reports.

The reaction of the referees to these suggestions for implementing the burden of proof proposal was extremely negative, and I have had similar reactions from other scientists. When I have made the suggestions to concerned citizens groups or the general public, however, the reaction has generally been favorable. This polarization is something which concerns me and which I think should concern the scientific community.

All of the referees were much concerned about false alarms from the early warning system. One suggests: "I also wonder when the public will start to look at these early warnings as unproductive, since it may in one month alone suggest that eating, drinking, and breathing may be exceedingly dangerous for a multitude of new discoveries. Overloading the system will occur based on our knowledge of what papers have appeared in the literature in the last few months requiring action."

Another referee says: "I think our present channels existing today are very accurate to take care of the alertness. As an example I would like to mention the case of the flame retardants, the saccharin, and the spray paint . . . I think it would be a waste of money and paper to create a so-called early warning system as described in this paper by Dr. Bross. It probably would have been very accurate to do what he is proposing ten years ago, but I think he is out of date."

A third referee says: ". . . the author can have very little idea of the high proportion of false alarms which occur in the more general field. The early publication of such alarms before adequate evidence is gathered could have serious effect on public confidence in scientists—one can cry 'wolf' too often."

Doubtless many, perhaps most, EHP readers would share this preoccupation with false alarms. From my contacts with concerned citizens, however, I can report that a "serious effect on public confidence in scientists" already exists. It is not, however, a result of scientists crying "wolf" too often. The citizens are concerned because relatively few scientists have been on the side of the public in efforts to obtain adequate protection against environmental hazards. Indeed, the citizens find that much of the time the scientific or medical establishment is on the other side of any effort to circumscribe the uses of technology. For instance, in the recent legislative battles over protecting the public against the potential hazards of recombinant DNA research, the lobbyists against "government interference" included the president of MIT, representatives of Harvard, Stanford, and Cornell, and spokesmen for various scientific societies. So while traditional scientists may give top priority to avoiding false alarms, the public gives top priority to getting protective action on real alarms.

Avoiding "false alarms" at all costs is a luxury that only "pure science" can afford. In "pure science" the usual way to avoid making a wrong statement is to make a nonstatement (but in very technical language). However, to protect the public against environmental hazards, actions are needed and not just empty statements. Taking action always involves nonnegligible risks, in part because inaction is itself a course of action. The dread of being accused of giving a false alarm and having one's reputation damaged often results in inaction. It is again a matter of inverted priorities. While reputation is important to a scientist, it is a small personal cost when the health and safety of other human beings is at stake. If factual evidence shows that a hazard exists, I believe a scientist has the responsibility of warning the public irrespective of the opinions of colleagues. Over the years, I have been accused at least a dozen times of sounding false alarms which subsequently turned out to be very real alarms. This has won me no medals from the establishment but I've saved a large number of lives this way.

The tendency of scientists to talk and temporize indefinitely instead of taking action on a public health issue has consistently worked to the advantage of proponents of hazardous uses of technology and against the public. This may not be a deliberate bias toward technology but it has the same effect. The Primacy Principle explicitly counterbalances this bias.

The article originally submitted to EHP was accompanied by an example of an early warning report. Readers who might like to see how the format for such a report would differ from a conventional paper will find this example (with some minor amplification) in the May 30, 1977 issue of the *Journal of the American Medical Association* 237: 2399). This early warning report by Bross and Natarajan concerns genetic damage from diagnostic radiation.

The editorial history of this article indicates the need for formats and reviewing procedures that would facilitate the communication on information on environmental hazards to the public. In this instance the publication was held up about a year. Other warning articles have been held much longer or delayed indefinitely. It is especially difficult for

authors to publish their findings if they are not well known, are not connected with a well-known institution, or lack special credentials. However, an early warning report should not be judged by the name of the author but by the data and methodology.

Although the report by Bross and Natarajan was rejected for a variety of reasons, none of them involved any specific faults in the data, the methodology, or the quantitative conclusions. The objections were to style, format, and trivia and not to substance. One reviewer was so annoyed that I had not cited his negative findings he cited them in his review. Another reviewer objected that there was no confirmatory report—an unreasonable requirement for an early warning report. Actually there are the independent, mutually confirmatory findings of Mancuso, Stewart, and Kneale which are coming out in *Health Physics*. Lack of comprehensive review of literature, lack of a general discussion of radiation hazards, and lack of other traditional trappings were other reasons for objections. Such irrelevant and persnickety reasons were given for keeping the news about genetic damage from ordinary diagnostic radiation from the public for a year.

There is nothing exceptional about this editorial history of a paper on the hazards of low levels of ionizing radiation except that the delay was so short. Other papers in this area have been blocked by the proponents of radiation technology for years and in some cases indefinitely. I have given a congressional committee documentary evidence of the partly successful attempt to block publication of the Mancuso, Stewart, and Kneale article (it was delayed until after funding was cut off "for lack of publications") and of the successful attempt to suppress a previous report of cancer deaths among the workers at the Hanford reprocessing plant. A reviewer chides me for my "jaundiced view of scientists" but when this sort of thing has been going on in the radiation area for more than two decades one gets a jaundiced view.

In part these efforts to block publication may be a matter of the research area. However whenever the technological hazards involve many millions of dollars, I have found that the game is played this way. The strategy of the proponents of hazardous technology is to delay or confuse the health issues by any and all means and they can always find some scientists to help them do this. The same reviewer says "In contrast, the cases that I can recall of delay in dealing with real hazards are few." On my part, I have seen very few instances of prompt and effective action to protect the public against carcinogens from products or processes that were of great economic importance. We still have not dealt effectively with the health hazards of cigarettes although the facts of the matter were clear 25 years ago when I just became involved.

A strong affirmation of the Primacy Principle and steps to implement it are, I believe, a necessary and useful first step toward giving the public the protection against environmental hazards that it so badly needs. As I told congressional committees on June 14 and June 17 of this year, cancer is a preventable disease and with effective primary prevention programs we could be well on our way to preventing it by the end of the century. To do this, however, we have to change the approaches and attitudes that have blocked action and progress in recent years and restructure our priorities to favor doing something about environmental hazards instead of just talking about them.

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